a2 38. (Amended) The method according to claim 33 [32] wherein the cell sample comprises T cells.

Please add the following claim.

a3 --59. The antibody according to claim 32, wherein the antibody is a monoclonal antibody.--

In the abstract

Delete the current Abstract and substitute therefor. --The present invention provides antibodies which specifically recognize apoptosis-modulating proteins. Further provided are a4 methods of detecting apoptosis-modulating proteins using the antibodies.--

II. REMARKS

Status of the claims

Claims 32-38 are pending in the case, following the election of Group IV in a communication filed on June 24, 1996 in response to the Restriction Requirement dated April 25, 1996. By virtue of this amendment, claims 1-31 and 39-58 are canceled without prejudice. Claims 32-38 have been examined and are rejected. These rejections are addressed in the appropriate sections below.

Generally, the claims are amended to define the invention more specifically and to correct errors pointed out by the Examiner or noted by the Applicants. In particular, claims were amended to provide proper antecedent basis for the recited language. In one claim, an amendment was made to correct claim dependency. The claim amendments are addressed in detail below.

The amendments to the claims are supported by the specification and no new matter has been introduced. Entry of these amendments is respectfully requested. Reexamination and reconsideration of the claims, as amended, are respectfully requested.

Summary of the invention

The claimed invention provides antibodies which recognize proteins, designated CDNs, which are members of the bcl family of apoptosis-modulating proteins, and which modulate apoptosis. The claimed invention further provides methods of detecting CDNs in biological samples. The method entails obtaining a cell sample, lysing the cells or making the cells permeable to antibodies, adding antibodies which recognize a CDN to the sample and allowing the antibodies to form complexes with the CDN, and, finally, detecting the CDN-antibody complexes formed.

Objections to the specification

The Examiner has pointed out that the status of any copending and/or parent and/or foreign priority documents listed in paragraph 1 of the specification must be updated. Accordingly, the specification has been amended to indicate the fact that the parent case, USSN 08/160,067 is abandoned.

Applicants acknowledge receipt of Substitute PTO Form 948. Formal drawings will be submitted upon allowance of the application.

The Examiner has objected to the Brief Description of Figure 7, because it does not indicate that the figure includes an amino acid sequence. Accordingly, Applicants have amended the description to comply with Examiner's requirements.

The Examiner has objected to the title of the invention as allegedly not being descriptive of the invention. Accordingly, Applicants have amended the title to describe the claimed invention.

The Examiner has objected to the Abstract of the Disclosure as allegedly not being descriptive of the claimed invention. To describe more accurately the claimed invention, Applicants have amended the Abstract. Applicants believe the amended Abstract complies with the Examiner's requirements.

The Examiner has objected to the specification as allegedly failing to provide proper antecedent basis for the claimed subject matter. In particular, the Examiner notes that claim 33 recites the limitation "lysing or permeabilizing" in line 5, "complex" in line 10 and "antibody-cdn complexes" in line 12. The Examiner alleges that there is insufficient antecedent basis in the specification for these limitations in claim 33. Applicants respectfully traverse. It is stated in the specification (page 12, lines 6-9) that methods of detecting proteins using antibodies are known in the art. These methods are well-known and protocols are widely available so that it is unnecessary to describe in the specification in detail the methods used. One of ordinary skill in the art would know how to find methods for lysing cells or permeabilizing them to antibodies. Furthermore, one of ordinary skill in the art would know that an antibody which recognizes a protein forms a complex with that protein, so that there is no need to state this in the specification. Claim 33, as amended, recites "antibody-CDN complexes". As with "complexes", that an antibody which would recognize a CDN would form a complex with that CDN is a standard art concept and therefore does not need to be elaborated on in the specification. Nevertheless, the specification has been amended to include the limitations of claim 33. Applicants therefore respectfully request that this objection be withdrawn.

The Examiner has further objected to the specification as allegedly providing insufficient antecedent basis for the limitation "T cells", recited in claim 38. The specification has now been

amended to include this limitation. Applicants respectfully request that the objection be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 32-38 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner notes that claim 32 is directed to a composition comprising a monoclonal or polyclonal antibody which recognizes a CDN but is substantially unreactive with other members of the bcl family. The Examiner alleges that claim 32 is indefinite in the recitation of "recognizes a CDN". The Examiner states that "the precise meaning of 'recognizes' and of the laboratory designation 'CDN' is not clear; nor do these terms have a commonly accepted meaning in the art". Applicants respectfully traverse. First, the term "recognize" as it relates to antibody recognition of an antigen, is indeed a commonly accepted term in the art. One need go no farther than a standard reference for protocols relating to molecular biology such as *Current Protocols in Molecular Biology* eds. Ausubel et al., Greene Publishing and Wiley-Interscience: New York (1987). In this standard laboratory manual, in Section 11, wherein protocols relating to immunological techniques are described, the terms "react with", "bind to" and "recognize" are used interchangeably. One of ordinary skill in the art would know that "recognize" in this sense describes the interaction between an antibody and an antigen, the result of which is complex formation. Therefore, Applicants submit that the term "recognize" carries an art-recognized meaning and request that the rejection be withdrawn. Nevertheless, for the sake of expediting prosecution, the claims have been amended in accordance with the Examiner's suggestions. Support for the amendments is found on page 10, lines 25–26, *inter alia*.

Secondly, regarding the term "CDN", CDN has been defined in the specification (page 5, lines 16-18) as being the proteins encoded by the cdns, which are clearly defined in the specification. CDN is further defined (page 6, lines 19-25) as encompassing functionally equivalent variants. While there is a requirement for a term recited in a claim to find support in the specification, there is no requirement that a term that is adequately defined in the specification have a commonly accepted art meaning. Since the requirement with respect to the term CDN finding support in the specification has been fulfilled, the rejection has been overcome. Nevertheless, the limitation requested by the Examiner has been added to the claim solely to expedite prosecution.

The Examiner further states that the terms "substantially unreactive" and the metes and bounds of "bcl family" cannot be ascertained from the disclosure. Applicants respectfully traverse. First, the term "substantially unreactive" is a term that would be understood by those of ordinary skill in the art to indicate antibodies that do not recognize proteins other than CDNs. Secondly, the bcl family of proteins is known and a reference describing the family members is given in the specification (page 3, lines 9-11). One of ordinary skill in the art would be able to determine whether an antibody recognized a CDN or not. Nevertheless, the claims, as amended, overcome this rejection.

Claims 33-38 are directed to a method of detecting the presence of a CDN protein in a biological sample. The Examiner has rejected claims 33-38 for allegedly being indefinite in the recitation of "a CDN protein" and "anti-cdns" and "CDN" for reasons recited above. Claim 33 has been amended to recite "anti-CDNs". Regarding the Examiner's allegation that recitation of CDN is indefinite, Applicants respectfully traverse. As pointed out in the preceding paragraph, the term CDN is defined in the specification. In particular, the Examiner suggests that the claim be rewritten to recite "an apoptosis-associated CDN protein having the amino acid sequences of CDN-1, CDN-2, CDN-3 and the derivative proteins". However, as already stated, the term

CDN, as defined in the specification encompasses derivatives of the protein including any portion which retains apoptosis modulating activity (page 6, lines 19-21). Therefore, functionally equivalent variants are part of the term as described and there is no need to reiterate this in the claims. This rejection is overcome by the amendment suggested by the Examiner.

The Examiner notes that the appropriate SEQ ID NO: designations should be inserted after each reference in the claims to a CDN protein. Applicants have amended claims 33, 34, 36 and 37 accordingly.

The Examiner alleges that claim 32 is indefinite in the recitation of "composition" because "only one element is recited, and a composition must recite two or more elements". Applicants respectfully traverse. No support is provided for this allegation. It seems that a composition "comprising" one well-defined component could contain numerous other components. When using the open-ended term "comprising," there is no requirement for enumeration of other components. For instance, buffers, salts or a variety of components could be present. However, in the interest of expediting prosecution and without admitting that the claim is indefinite, Applicants have amended the claim. Applicants therefore request that this rejection be withdrawn.

Claims 35, 37 and 38 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In particular, the Examiner notes that claims 35 and 37 recite "nucleotide sequence" and that this phrase lacks antecedent basis in the claims. Claims 35 and 37 have been amended to recite "a nucleotide sequence". The Examiner further notes that claim 38 lacks antecedent basis in the claims for recitation of "The method according to claim 32". Accordingly, Applicants have amended claim 38 to correct the claim dependency.

Applicants believe that all the rejections on the grounds of indefiniteness have been adequately addressed and that the above amendments to the claims overcome the rejections. Therefore, it is respectfully requested that these rejections under § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

Claims 33-38 are rejected under 35 U.S.C § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner notes that the method as claimed relies on immunologic detection of CDN protein in a cell sample which has been lysed or permeabilized, and that such a method assumes that the protein is present intracellularly in sufficient amounts to be detected. The Examiner states that "the specification does not disclose whether the CDN protein accumulates intracellularly in biological samples or is secreted, or if the protein is in a form that is available to and bindable by antibodies made against recombinantly expressed CDN protein (the only enabled method for making anti-CDN protein antibodies)". The Examiner further states that "it is uncertain whether [the CDN protein] is present in sufficient quantity" to be detected, and concludes that undue experimentation would be required to enable the method of detecting a CDN protein, including methods wherein the sample comprises T cells. Applicants respectfully traverse. Applicants respectfully point out that it is incumbent upon the Patent Office to explain why it doubts the truth or accuracy of the disclosure, which is presumed accurate. In re Marzocchi, 169 USPQ 367 (CCPA 1971); MPEP 2163.04. In the absence of evidence casting doubt on a claimed invention, Applicants are under no obligation to rebut the rejection.

However, solely as a courtesy to the Examiner and to expedite prosecution, Applicants present arguments and evidence in support of the disclosure.

In the discussion of the nucleotide and translated amino acid sequence of cdn-1 (page 19, lines 6-15), it is noted that the protein encoded by cdn-1 appears to be an intracellular protein in that it contains neither a hydrophobic signal peptide nor N-linked glycosylation sites. The presence of these features is generally indicative of a secreted protein, and lack thereof is generally indicative of a protein that remains associated with the cell. Moreover, cdn-1 encodes a protein that is predicted to contain a hydrophobic C-terminus, a feature shared by all bcl-2 family members except LMW5-HL, suggesting that, like bcl-2, it may be localized to a membrane-bound organelle. Taken together, these sequence features are suggestive of a protein that remains cell-associated and therefore there is a reasonable expectation that CDNs would be detectable by the methods of claims 33-38.

Indeed, as shown in the accompanying Declaration Under Rule 132, submitted herewith as Exhibit A, CDNs are recognized in cell lysates by antibodies generated against a CDN.

The Examiner further states that the specification does not disclose whether the CDN protein is "in a form that is available to and bindable by antibodies made against recombinantly expressed CDN protein (*the only enabled method of making anti-CDN protein antibodies*)" (emphasis added). Applicants respectfully traverse. In the specification (page 12, lines 3-6), it is stated that suitable antibodies are generated by using CDNs as antigens or peptides encompassing the CDN regions that lack substantial homology to the other gene products of the bcl family. CDNs as defined in the specification, are not limited to recombinantly expressed CDN proteins. Rather, the source of CDNs can be CDNs expressed either by the recombinant DNA or from biological sources such as tissues (bridging paragraph of pages 10-11). One of ordinary skill in the art would have no reason to expect that antibodies thus generated would fail to recognize CDNs in a cell sample.

The Examiner goes on to state that "it is uncertain whether [CDN protein] is present in sufficient quantity or in a form which is available for detectable binding to antibodies", and argues that in view of "the limited guidance in the specification and the unpredictability associated with the presumed intracellular amount and availability of the protein, undue experimentation would be required to enable the method of detecting a CDN protein". Applicants respectfully traverse. As stated in the preceding paragraph, antibodies generated according to standard methods and using CDN proteins or peptide fragments thereof could reasonably be expected to recognize proteins in a cell sample. Regarding "availability", it is unclear what the Examiner intends. If the Examiner is concerned about possible sequestration of a CDN protein in a membrane, this is not typically a problem, since the conditions under which cells are lysed can be adjusted to effect solubilization of membranes and hence, membrane proteins. The Examiner states that it is uncertain whether sufficient amounts of CDN protein would be present in a cell sample to allow detection. Again, it is incumbent upon the Examiner to provide evidence casting doubt on the claimed invention in order to support such a rejection. This has not been provided. In contrast, it is known in the art that the prototype bcl family member, bcl-2, has been detected in cell samples. It is therefore not unreasonable to expect that CDNs would be detectable in cell samples. Furthermore, even cellular proteins which are known to occur in very low abundance in a cell are detectable by methods known to those of ordinary skill in the art. In addition, the ability to readily determine the presence of CDNs in a cell line by Western blot (as shown in the accompanying Declaration) indicates that there should be no doubt as to the ability to detect CDNs in other cell types.

The Examiner states that detection of "nucleotides" as recited in claims 35 and 37, is not enabled. Applicants have amended claims 35 and 37 accordingly to recite "CDN encoded by a nucleotide sequence". The claims as amended are enabled for the reasons stated in the preceding paragraph.

The Examiner states that claim 38 is not enabled because "it is unpredictable that T cells produce detectable quantities of CDN protein. Applicants respectfully traverse for the reasons stated above in response to the rejection of claims 33-38. The Examiner has presented no clear evidence or reasons why one would *not* expect the claimed method to allow detection of CDN proteins in T cells. The evidence in the art and the attached Declaration indicate that there would be no doubt.

Claims 32-38 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is allegedly not enabling for antibodies that bind to any CDN other than those for which the sequence is disclosed. The Examiner states that the specification does not appear to specifically define the metes and bounds of CDN protein. Applicants respectfully traverse. It is well within the ability of one of ordinary skill in the art to determine whether a protein having an amino acid sequence different from those disclosed in the specification would react with an antibody generated against a CDN having an amino acid sequence disclosed in the specification. A variety of references are available in which protocols outlining immunoassays are described in detail, including, for example Harlow and Lane, eds. *Antibodies: A Laboratory Manual* (1988) Cold Spring Harbor Laboratory. These are standard protocols, known in the art, and determination of cross-reactivity does not entail undue experimentation. Nevertheless, the claims have been amended to more clearly define the CDN proteins recognized by the antibodies.

Claims 33 and 38 are rejected for reasons set forth in the objections to the specification. Applicants respectfully traverse on the grounds stated in response to the objections to the specification.

All the rejections on the grounds of enablement have been adequately addressed by amendment or explanation. Therefore, it is respectfully requested that these rejections under §112, first paragraph, be withdrawn.

III. CONCLUSION

Applicants submit that the above discussion is fully responsive to all grounds of objection and rejection set forth in the Office Action. In view of the comments above, Applicants respectfully request that all outstanding rejections be withdrawn, and that the pending claims, as amended, be allowed.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 813-5695.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 20, 1997

Respectfully submitted,

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